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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Non-Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Yvette Alvarez-Perez — Date 12/9/03

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.	:	10/646,904
Applicant	:	Herbert Irschik et al.
Filed	:	August 22, 2003
Title	:	Use of Disorazoles and Their Derivatives for the Treatment of Benign And Malignant Oncoses
Attorney Docket No.	:	(old) 103832-510-PRO; (new) 103832-510-NP

Mail Stop Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF ENGLISH TRANSLATION OF PROVISIONAL APPLICATION UNDER 37 CFR 1.78(a)(5)

Sir:

The above-identified patent application claims priority from Provisional Application No. 60/405,594 filed on August 24, 2002 under 35 U.S.C. 119(e). The Provisional Application was filed in a German. Applicants submit herewith an English translation of the non-English provisional application and a statement that the translation is accurate under 37 CFR 1.78(a)(5).

The Commissioner is authorized to charge any required fees to Goodwin Procter LLP Deposit Account No. 06-0923.

Respectfully submitted for Applicants,

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UNITED STATES PATENT AND TRADEMARK OFFICE

I, Susan ANTHONY BA, ACIS,

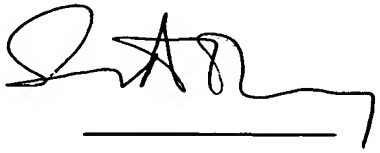
Director of RWS Group plc, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That the translator responsible for the attached translation is well acquainted with the German and English languages.

3. That the attached is, to the best of RWS Group plc knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in The United States of America on 24 August 2002 under the number 60/405,594 and the official certificate attached hereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.



For and on behalf of RWS Group plc

The 2nd day of October 2003

JC950 U.S. PTO
08/24/02

08-26-02 60405594 - 082402

Express Mail No. EL 753206969 US

J1036 U.S. PTO
60/405594
08/24/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of Herbert Irschik et al.\

Filed: herewith

For: Use of Natural Materials from the Disorazole Group, etc. (in German)

Attorney's Docket 0691-088

Attorney's Customer No. address 23622

Commissioner of Patents
Washington DC 20231

Sir:

This is an application data sheet for the enclosed new **provisional** application by the following inventors, all citizens of Germany, and all residing in Germany:

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Please charge the $160 provisional application fee to deposit account 060923.

Respectfully submitted

(signature)

Gabriel P. Katona, Reg. No. 20,829

Use of natural substances from the group of the disorazoles and its d rivatives for the treatment of benign and malignant oncoses.

Description of the invention:

It is known that natural substances of the group of the disorazoles are isolated from the bacterium of the strand Sorangium cellulosum /1/. For the disorazole A1, it was reported that it possesses cytotoxic activity in simple cellular models /2/. It has now been found that, surprisingly, especially the disorazoles E1 and D1 possess outstanding cytotoxic activity with regard to various human tumor cell lines. The inventors have been able to show that the antiproliferative effect of the claimed disorazoles rests on an effective inhibition of tubulin polymerization. It has been determined for the claimed disorazoles that this effect is cell cycle specific. The disorazole E1 is among the disorazoles investigated the most potent compound with regard to the inhibition of the division of human tumor cell lines. More particularly, disorazole E1 is highly active even against cell lines resistant to Taxol and vindesines.

The compounds according to the invention are therefore suitable for employment as medicaments for the treatment of benign and malignant oncoses or other antiproliferative disorders in humans and animals. A further conceivable application would be for example the prevention of inflammations in the case of the treatment of a patient using stent technology. The compounds according to the invention can be employed as an individual substance or in combination with further cytotoxic substances, e.g. cisplatin, carboplatin, doxorubicin, ifosfamide, cyclophosphamide, 5-FU, methotrexate and in particular in combination with inhibitors of signal transduction, for example, Herceptin, Glivec or Iressa, but not restricted thereto.

Synthetic and semisynthetic analogs of disorazole E1 and D1 also possess antiproliferative action. By means of specific modification of the molecular shape, important properties such as biological inhibitory action, stability and biophysical properties can be modulated. In this manner, therapeutically valuable derivatives of the starting compounds are obtainable.

The medicaments according to the invention can be administered as liquid, semisolid and solid pharmaceutical forms. This is carried out in the manner suitable in each case in the form of aerosols, oral powders, dusting powders and epipastics, tablets with or without coatings, emulsions, foams, solutions, suspensions, gels, salves, pastes, pills, pastilles, capsules or suppositories.

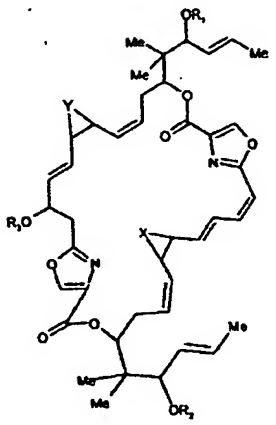
The medicaments according to the invention can be administered in a suitable administration form to the skin, epicutaneously as a solution, suspension, emulsion, foam, ointment, paste or patch; via the oral and buccal mucosa, bucally, lingually or sublingually as an uncoated tablet, pastille, coated tablets, linctus or gargle; via the gastric and intestinal mucosa, enterally as an uncoated tablet, coated tablets, capsule, solution, suspension or emulsion; via the rectal mucosa, rectally as a suppository, rectal capsule or ointment; via the nasal mucosa, nasally as drops, ointment, or spray; via the bronchial and alveolar epithelium, pulmonarily or by inhalation as an aerosol or inhalant; via the conjunctiva, conjunctivally as eye drops, eye ointment, eye tablets, lamellae or eye lotion; via the mucosae of the genital organs, intravaginally as vaginal suppositories, ointments and flush, intrauterinely as a uterine pessary; via the efferent urethras, intraurethrally as a flush, ointment or medicated probe; into an artery, intraarterially as an injection; into a vein, intravenously as an injection or infusion; into the skin, intracutaneously as an injection or implant; under the skin, subcutaneously as an injection or implant; into the muscle, intramuscularly as an injection or implant; into the abdominal cavity, intraperitoneally as an injection or infusion.

The invention further includes technological processes for isolating and synthesizing the compounds of the invention.

If the compounds of the general structure I according to the invention have at least one asymmetric center, they can be present in the form of their racemates, in the form of the pure enantiomers and/or diastereomers or in the form of mixtures of these enantiomers and/or diastereomers, namely both in substance and as pharmaceutically acceptable salts of these compounds. The mixtures can be present in any desired mixing ratio of the stereoisomers.

If possible, the compounds according to the invention can be present in the form of the tautomers.

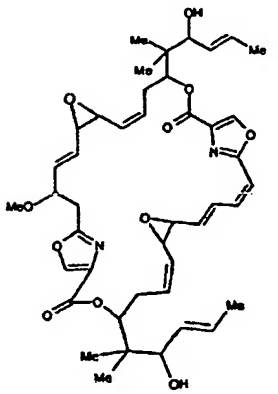
General formula I as per claim:



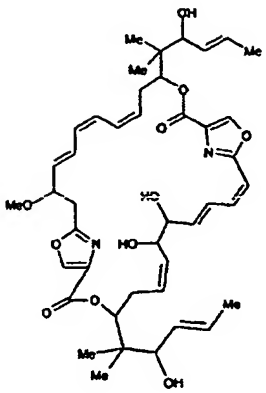
R1, R2, R3, H, alkyl, COalkyl, aralkyl, X, Y, O, S, NH, N-alkyl, 2xOH, -

Operative examples:

Disorazole E1



Disorazole D1



Biological data:

Inhibition of tubulin polymerization

Bovine tubulin, 30% MAPS

	IC_{50} [μM]
Disorazole E1	1.93
Disorazole D1	3.19

Inhibition of selected tumor cell lines

Disorazole E1

Tumor cell line	Tissue	IC_{50} [μg/ml]
HT29	colon	8.6×10^{-5}
ASPC1	pancreas	2.5×10^{-5}
A172	brain	2.4×10^{-4}
U118MG	brain	9.1×10^{-7}
PC3	prostate	1.4×10^{-4}
DU145	prostate	6.7×10^{-7}
U373MG	brain	2.8×10^{-5}
C6	brain	5.1×10^{-6}
T47D	breast	1.4×10^{-6}
KB/HeLa	cervix	3.8×10^{-7}
SK-OV-3	ovarial	1.8×10^{-6}
RKOP27		3.2×10^{-7}

Activity with regard to resistant tumor cell lines

IC_{50} in μM

Cell line	Disorazole E1	Vindesines	Taxol
L12 wt	0.0001	0.001	0.006
LT12mdr	0.004	0.26	0.40
L1210 wt	0.0005	0.02	0.06
L1210 mdr	0.002	2.30	> 5
L1210 vcr	0.006	> 5	> 5
P388 wt	0.0004	0.01	0.04
P388 ADR	0.001	1.10	> 5

wt: wild type

References

/1/ R. Jansen, H. Irschik, H. Reichenbach, V. Wray, G. Höfle, Liebigs Ann. Chem., (1994), (8), 759-773 - Antibiotics from gliding bacteria. LIX. Disorazoles, highly cytotoxic metabolites from the sorangicin-producing bacterium Sorangium cellulosum, strain So ce12.

/2/ H. Irschik, R. Jansen, K. Gerth, G. Höfle, H. Reichenbach, J. Antibiot. (1995), 48(1), 31-35 - Disorazol A, an efficient inhibitor of eukaryotic organisms isolated from myxobacteria.